Computer simulation of glycolsis a comperative study of the control of glycolysis in fetal and adult rat liver

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6. GENERAL DISCUSSION.

The purpose of these studies was to analize control phenomena in the glycolytic pathway. These investigations were mainly carried out with the steady state program as described in chapter 5. It turned out that in fetal tissue the key enzyme is hexokinase. In the adult situation the key enzymes are hexokinase (aerobic situation) and phosphofructokinase (anaerobic situation). An enzyme is rate controlling if the glycolytic flux is determined by the kinetics of that particular enzyme. If for instance under the same circumstances the concentration of hexokinase is doubled , a two fold rise of the glycolytic flux will result. No change in glycolytic flux will occur if another (not rate controlling) enzyme concentration is varied. Therefore as a definition of a control point we can use the change in steady state flux as a consequence of the change in enzyme concentration i.e. $dJ/d[E]$.

The simulation of the transition aerobic to anaerobic glycolysis, shows the relative activities of the enzymes. In fig. 3 the relative changes of the concentrations of the glycolytic intermediates are shown as a function of time. F6P is almost immediately at its anaerobic value, because PGI is a very active enzyme. The ratio GLYP/DHAP remains about the same wich illustrates that TPI is very active and operates near equilibrium. The concentrations of 1,3PGA, 3PGA, 2PGA, PEP and PYR do not change very much, therefore we may conclude that the enzymes PGK, PGM, ENOL and PK are not limiting during the transition. However FDP, GLYP and DHAP accumulate to relatively high values. This happens because the NAD to NADH ratio decreases as a consequence of the LDH kinetics and therefore GAPDH becomes a limit-

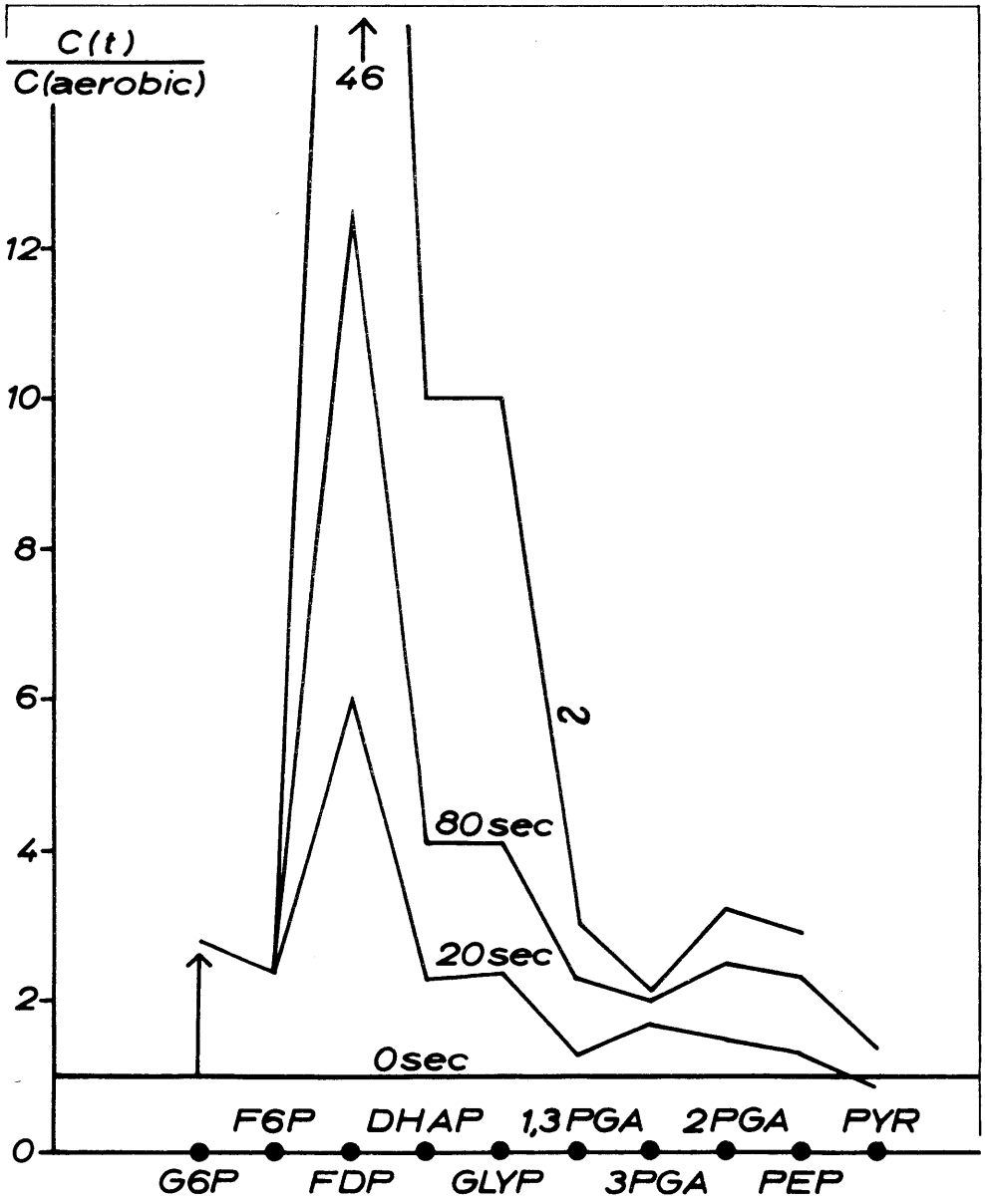

figure 3.

Ratio of concentrations of intermediates to the steady state aerobic values at 0, 20, 80 and ∞ seconds after the transition from aerobic to anaerobic conditions.

ing enzyme during the transition. The glycolytic flux will attai its anaerobic value if the intermediates have reached their anae obic concentrations.In our model this time is determined by the GAPDH mechanism.

The control points in metabolic regulation can be found with the steady state program, which is a very fast program. This is very important because this program can easily be enlarged with connecting metabolic pathways, which is of great value for future research. Thus the computer program is not the limiting factor in studying metabolic regulation.

Furthermore it is obvious from these investigations that enzymes which are not rate limiting can be represented by simple mechanisms. In this way it is possible to reduce the system which makes it easier to handle. The simulation studies of Garfinkel and coworkers of beef heart supernatant preparation demonstrates clearlythat the results are not improved very much by introducing detailed mechanisms for the individual enzymes. The computer time necessary to simulate the transition aerobic-anaerobic glycolysis is determined by the differential equation which is the most "stiff" equation. Most of the time this differential equation represents an intermediate which is very low in concentration (for instance 1,3 PGA in glycolysis). If it can be assumed that this intermediate remains in steady state this differential equation can be omitted and larger steplenghts can be applied. In this way it is possible to speed up the program. In our case 45 minutes computer time was needed to simulate 80 sec. of real reaction time.